# Complete Summary

## GUIDELINE TITLE

WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses.

## BIBLIOGRAPHIC SOURCE(S)

World Health Organization (WHO). WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva: World Health Organization (WHO); 2009 Aug 20. 83 p. [23 references]

## GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

- Pandemic (H1N1) 2009 influenza virus infection
  - Uncomplicated
  - Complicated or severeÂ influenza
- Other influenza virus infections

### GUIDELINE CATEGORY

Management
Prevention
Risk Assessment
Treatment

## CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Geriatrics
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine
Pulmonary Medicine

## INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Nurses
Pharmacists
Physician Assistants
Physicians
Public Health Departments

## GUIDELINE OBJECTIVE(S)

To provide a basis for advice to clinicians on the use of the currently available antivirals for patients presenting with illness due to influenza virus infection, as well as the potential use of the medicines for chemoprophylaxis

## TARGET POPULATION

- At risk populations: infants and children aged <5 years, the elderly, nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, human immunodeficiency virus (HIV) infection, or other diseases
- Otherwise healthy persons

## INTERVENTIONS AND PRACTICES CONSIDERED

### Management/Treatment/Prophylaxis

1. Oseltamivir
2. Zanamivir
3. Amantadine
4. Rimantadine
5. Other interventions such as ribavirin, immunoglobulin, and interferons (not licensed for the treatment of influenza and should only be used in the context of prospective data collection)

**Note**: The use of antibiotics, oxygen and ventilator therapy, and other modalities for the treatment of pneumonia, acute lung injury, adult respiratory distress syndrome (ARDS), septic shock, multi-organ failure, and other severe complications requiring critical care intensive care management is beyond the

scope of the current antiviral guidelines document. It is recommended that clinicians consult national guidelines for recommendations regarding the use of these therapies.

### MAJOR OUTCOMES CONSIDERED

- Treatment
    - Mortality
    - Hospitalization
    - Duration of hospitalization
    - Time to alleviation of symptoms
    - Time to return to normal activity
    - Complications (lower respiratory tract infection, otitis media)
    - Influenza cases prevented
    - Serious adverse events
    - Mild adverse eventsÂ
    - Drug-related adverse events
    - Drug resistance
    - Viral shedding
    - Cost of drugs
- Prophylaxis
    - Influenza cases prevented
    - Influenza-like illness cases
    - Mortality
    - Hospitalization
    - Complications (lower respiratory tract infection, otitis media)
    - Serious adverse events
    - Mild adverse event
    - Drug-related adverse events
    - Drug resistance
    - Viral shedding
    - Cost of drugs

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The search strategy sought to identify relevant systematic reviews assessing the use of oseltamivir, zanamivir, amantadine, and rimantadine in the treatment and prophylaxis of influenza. Once systematic reviews were identified, searches were also conducted for randomized controlled trials in order to identify any additional trials not included in the reviews. These searches were limited to the years 2006 to 2009.

In addition to randomized controlled trials, a search was also conducted for observational studies, in particular those assessing outcomes not included in the systematic reviews, such as influenza complications, adverse events, and mortality. Case reports and studies including fewer than 10 subjects were excluded from further consideration on the basis of title and abstract review.

Summaries of all identified systematic reviews, individual trials, and observational studies were sent to members of the Guidelines group before the June 2009 meeting, and they were asked to identify any important evidence that had not been included.

Searches were also conducted for any papers discussing modeled evaluation of influenza, including assessment of cost-effectiveness of the drugs and impact of interventions to control pandemic spread.

All searches were conducted in May 2009.

## NUMBER OF SOURCE DOCUMENTS

Not stated

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

### GRADE Evidence Assessment Criteria

- **High**: Further research is very unlikely to change the confidence in the estimate of effect.
- **Moderate**: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
- **Low**: Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
- **Very low**: Any estimate of effect is very uncertain.

## METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

### Preparation of the Background Documentation

Background documentation was prepared in order to assist the World Health Organization (WHO) Rapid Advice Guidelines Group on Influenza revise earlier guidance on the treatment and prophylaxis of avian influenza (H5N1) infection in humans.

Summaries of the best available evidence were prepared to inform questions regarding the use of antivirals for treatment and prophylaxis in a range of populations (adults, elderly, children, 'at-risk'). The sensitivity of the virus and case fatality of the illness were taken into consideration.

### Identification of Important Outcomes

A list of potential outcomes to be considered by the panel was initially developed for the rapid guidelines for avian H5N1 influenza. These outcomes were ranked by the Guidelines group, who were also requested to identify any relevant critical outcomes not included in the list. The group members were asked to identify which outcome they felt were critical, important but not critical and not important. The Group members were then asked to score the outcomes, using numbers corresponding to the GRADE importance of outcomes, where 7-9 indicated the outcome was critical for a decision, 4-6 indicated it was important, and 1-3 indicated it was not important. The individual scores were discussed and disagreements were resolved by consensus. Outcomes were included roughly in order of their relative importance in evidence tables and outcomes that were considered not important (a score of 3 or less) were not included.

### Selection Criteria, Data Collection, and Judgements

Systematic reviews were used to summarize the evidence from randomized trials. The most recent reviews of good quality were focused upon and were supplemented with additional data from other reviews when necessary.

Evidence profiles based on the systematic reviews were created using the GRADE approach using GRADE profiler software (version 3.2.2). Using this approach, assessments of the quality of evidence for each important outcome take into account the study design, limitations of the studies, consistency of the evidence across studies, the directness of the evidence, and the precision of the estimate. A liberal approach to assessment of study limitations was taken and the quality of evidence was not lowered because of reporting limitations, such as not clearly reporting whether there was concealment of allocation in trials. Three main criteria were used for assessing trial limitations: concealment of allocation, blinding, and follow-up. If most of the evidence for an outcome (based on the weight given to each study in the meta-analysis) came from trials that did not have serious limitations, the overall assessment for that outcome was that there were no important limitations.

Because all of the evidence in the reviews was based on seasonal influenza and was thus indirect for pandemic influenza, this aspect of the GRADE profile was scored accordingly, resulting in 'moderate' or 'low' classification of evidence.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations were drafted according to the GRADE method for assessing quality of evidence and strength of recommendations. A guideline panel comprising international scientists and experts in clinical treatment of influenza, guideline methodology, basic research, policy making, pharmacology and virology

was convened in June 2009. The panel was asked to identify critical clinical outcomes for the purposes of making the recommendations.

The panel reviewed the evidence summaries and the draft guideline and made recommendations. All recommendations were based on consensus.

Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs and values and preferences, described in the "Remarks" for each recommendation (Refer to "Major Recommendations" field). "Values" are the desirability or preference that individuals exhibit for a particular health state. Individuals usually assign less value to and have less preference for more impaired health states (e.g., death or dependency after a stroke) compared to other health states (e.g., full health or having a very mild stroke without serious sequelae). In this document, the term "values" refers to the relative worth or importance of a health state or consequences (benefits, harms and costs) of a decision.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendations are classified as "strong" or "weak," as recommended in the GRADE methodology.

**Strong** recommendations can be interpreted as:

- Most individuals should receive the intervention.
- Most well-informed individuals would want the recommended course of action and only a small proportion would not.
- Could unequivocally be used for policy making.

**Weak** recommendations can be interpreted as:

- The majority of well-informed individuals would want the suggested course of action, but an appreciable proportion would not.
- Widely varying values and preferences.
- Policy making will require extensive debates and involvement of many stakeholders.

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After the meeting, the guideline was revised by the World Health Organization (WHO) secretariat according to the recommendations from the panel and

circulated to the panel members for review. Comments were reviewed by the WHO secretariat and were incorporated into the final version.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The rating schemes for the quality of the evidence (very low, low, moderate, high) and the strength of the recommendations (weak, strong) are defined at the end of the "Major Recommendations" field.

**Table. Use of Antivirals for Treatment of Influenza** (Numbers refer to the specific recommendations within this document)

<table>
<tr><th>Population</th><th>Pandemic (H1N1) influenza virus 2009</th><th>Multiple co-circulating influenza A sub-types or viruses with different antiviral susceptibilities</th><th>Sporadic zoonotic influenza A viruses including H5N1</th></tr>
<tr><td colspan="4">Mild to moderate uncomplicated clinical presentation</td></tr>
<tr><td>At-risk[a] population</td><td>Oseltamivir or zanamivir (04)</td><td>Zanamivir, or oseltamivir plus M2 inhibitor[b] (10)</td><td>Oseltamivir or zanamivir</td></tr>
<tr><td>Otherwise healthy[c]</td><td>Need not treat (03)</td><td>Need not treat (03)</td><td>Oseltamivir</td></tr>
<tr><td colspan="4">[a]Infants and children aged less than 5, the elderly (>65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, human immunodeficiency virus (HIV) infection or other diseases.<br>[b]Amantadine should not be used in pregnant women (recommendation 12).<br>[c]All those not covered by the at-risk definition above</td></tr>
<tr><td colspan="4">Severe or progressive clinical presentation[d]</td></tr>
<tr><td>At-risk[a] population<br>Otherwise healthy[c]</td><td>Oseltamivir (01) (zanamivir should be used where virus is known to be resistant to oseltamivir, or if oseltamivir unavailable) (02)</td><td>Oseltamivir plus M2 inhibitor[b], or zanamivir (05, 06, 07)</td><td>Oseltamivir plus M2 inhibitor</td></tr>
<tr><td colspan="4">[d]See section 2 "Case Description" in the original guideline document. Would include all patients requiring hospitalization.</td></tr>
</table>

### Treatment of Seasonal or Pandemic Influenza: Recommendations for Use of Antivirals

**Influenza Pandemic (H1N1) 2009 Influenza Virus Infection**

Context: Treatment of patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009 virus, where clinical presentation is severe or progressive and antiviral medications for influenza are available.

**Recommendation 01**: Patients who have severe or progressive clinical illness should be treated with oseltamivir. **(Strong recommendation, low quality evidence)** Treatment should be initiated as soon as possible. Consideration may be given to the use of higher doses up to 150 mg twice daily (bid), and longer duration of treatment depending on clinical response.

This recommendation applies to all patient groups, including pregnant women, and young children <5 years, including neonates.

Treatment should be started as soon as possible (laboratory confirmation of influenza virus infection is not necessary for the initiation of treatment). The evidence from clinical trials suggest most patients benefit from treatment commencing within 48 hours of symptoms, but experience from use in patients with H5N1 virus infection and severe lower respiratory tract disease suggests that later initiation of treatment may also be effective, whenever viral replication is present or strongly suspected.

In patients with severe or progressive illness not responding to normal treatment regimens, higher doses of oseltamivir and longer duration of treatment may be appropriate, although there is no clinical trial evidence to show benefit. An adult dose of 150 mg bid is being used in some situations.

***Remarks***

This recommendation takes account of:

- The concern about the increased risk of severe complications or death from influenza in this context.
- The evidence from randomized controlled trials that shows a reduction of approximately one day in symptoms in outpatients, and evidence from observational studies in all patients that demonstrates a reduction in progression to severe disease and hospitalization in patients treated with antivirals.
- The ease of use and suitability of oseltamivir compared to other currently available neuraminidase inhibitors, i.e., oral administration versus inhaled.
- The opportunity cost of providing antivirals to these patients is considered low.

**Recommendation 02**: In situations where (1) oseltamivir is not available or not possible to use, or (2) if the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir, patients who have severe or progressive clinical illness could be treated with zanamivir. **(Strong recommendation, very low quality evidence)**

***Remarks***

This recommendation takes account of:

- The need to offer alternative treatment to patients with severe or progressive illness in the absence of oseltamivir or if the virus is known to be resistant to oseltamivir.
- The practical difficulties in administering zanamivir to severely ill patients in its current dosage form.

Context: Treatment of patients with confirmed or strongly suspected but uncomplicated illness due to pandemic influenza virus infection, and antiviral medications for influenza are available.

**Recommendation 03**: Patients not in 'at risk' groups (defined below) who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. **(Weak recommendation, low quality evidence)**

Risk groups are defined as: infants and children aged less than 5, the elderly (>65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, human immunodeficiency virus (HIV) infection or other diseases.

***Remarks***

This recommendation takes account of:

- The consideration of the potential opportunity cost of providing antivirals on a large scale to the community compared with taking public health measures to manage an outbreak.
- The concern about the potential development of resistant viruses that might transmit from person to person.

**Recommendation 04**: Patients in 'at-risk' groups, with uncomplicated illness due to influenza virus infection, should be treated with oseltamivir or zanamivir. Treatment should be initiated as soon as possible following onset of illness. **(Strong recommendation, very low quality evidence)**

***Remarks***

This recommendation takes account of:

- The concern about the increased risk of severe complications or death from influenza in this patient group.
- The consideration of the potential opportunity cost of providing antivirals to this limited group, compared with taking public health measures to manage a pandemic.
- The evidence from randomized trials that shows a reduction of approximately one day in symptoms in outpatients, and evidence from observational studies that demonstrates a reduction in progression to severe disease and hospitalization in patients treated with antivirals.

Â **Other Influenza Virus Strains**

Context: Treatment of patients with confirmed or strongly suspected infection with seasonal influenza virus, where antiviral susceptibility is known, and where clinical presentation is severe or progressive and antiviral medications for influenza are available.

**Recommendation 05**: Patients who have severe or progressive clinical illness due to oseltamivir-susceptible and M2 inhibitor-susceptible virus might be treated with both oseltamivir and either amantadine or rimantadine. **(Weak recommendation, very low quality evidence)**

***Remarks***

This recommendation takes account of:

- In vitro and animal model studies showing synergistic antiviral effects with the combination for dually susceptible strains compared to individual treatments. However, if clinicians choose to use combination treatment, whenever possible this should be done in the context of prospective clinical and virological data collection.

**Recommendation 06**: Patients who have severe or progressive clinical illness due to oseltamivir-resistant and M2 inhibitor-resistant virus should be treated with zanamivir. **(Strong recommendation, very low quality evidence)**

***Remarks***

This recommendation takes account of:

- The severity of the illness, and that zanamivir is the only alternative licensed antiviral drug.

**Recommendation 07**: In situations where there are co-circulating influenza A virus subtypes (even if there is probable or known oseltamivir resistance) patients who have severe or progressive clinical presentation should be treated with oseltamivir and either amantadine or rimantadine. **(Strong recommendation, very low quality evidence)**

This recommendation applies to all patients including pregnant women, in whom the risks of severe illness are likely to outweigh the risk of adverse events during treatment. However, there is a lack of evidence supporting use of amantadine or rimantadine in neonates.

***Remarks***

This recommendation takes account of:

- The concern about the increased risk of severe complications or death from influenza in this context.
- The need to commence treatment with at least one active agent.

- The probability that the virus will be resistant to one or other classes of antivirals. If laboratory data confirm drug resistance in the infecting strain, then the inactive drug should be stopped.
- The evidence from pharmacokinetic studies and animal studies that show combination therapy is safe.

**Recommendation 08**: In situations where the circulating influenza A virus has probable or known M2 inhibitor resistance (including pandemic [H1N1] 2009), patients who have severe or progressive clinical presentation should not be treated with amantadine or rimantadine (alone or in combination with other medicines). **(Strong recommendation, low quality evidence)**

***Remarks***

This recommendation takes account of:

- The concern about adverse effects of a treatment likely to be ineffective.

Context: Treatment of patients with confirmed or strongly suspected but uncomplicated illness due to seasonal or pandemic influenza virus infection, where antiviral sensitivity is known, and antiviral medications for influenza are available.

**Recommendation 09**: Patients not in 'at risk' groups who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. **(Weak recommendation, low quality evidence)**

***Remarks***

- As for recommendation 3 above

**Recommendation 10**: In situations where there are co-circulating influenza A virus subtypes (even when these include probable or known oseltamivir resistance), patients in 'at-risk groups' with uncomplicated illness due to confirmed or strongly suspected seasonal influenza virus infection should be treated with zanamivir, or with oseltamivir plus amantadine or rimantadine. **(Weak recommendation, very low quality evidence)**

This recommendation does not apply to pregnant women (see Recommendation 12 below).

***Remarks***

This recommendation takes account of:

- The need to provide potentially effective treatment to vulnerable patients.
- The consideration of the potential opportunity cost of providing antivirals to this limited group, compared with taking public health measures to manage a pandemic.

**Recommendation 11**: Where the most prevalent virus is probably or known to be oseltamivir-resistant, pregnant women with uncomplicated illness due to

seasonal influenza virus infection might be treated with zanamivir. **(Weak recommendation, very low quality evidence)**

**Recommendation 12**: Pregnant women and children aged less than 1 year with uncomplicated illness due to influenza virus infection should not be treated with amantadine or rimantadine. **(Strong recommendation, very low quality evidence)**

***Remarks***

This recommendation takes account of:

- The concern about the increased risk of adverse events due to amantadine in pregnant women and lack of evidence supporting use in young children.

**Recommendation 13**: Where the most prevalent virus is probably or known to be oseltamivir-resistant, immunosuppressed patients with seasonal influenza virus infection should be treated with zanamivir plus rimantadine. **(Weak recommendation, low quality evidence)**

***Remarks***

This recommendation takes account of:

- The need to provide potentially effective treatment to vulnerable patients.

**Chemoprophylaxis of Influenza: Recommendations for Use of Antivirals**

Context: Use of antivirals as chemoprophylaxis of pandemic (H1N1) 2009 influenza.

**Recommendation 14**: Where the risk of human-to-human transmission of influenza is high or low and the likelihood of complications of infection is high (either due to the strain or baseline risk of the exposed group) oseltamivir or zanamivir might be used as post exposure chemoprophylaxis for the affected community or group, individuals in 'at risk' groups or health care workers. **(Weak recommendation, moderate quality evidence)**

***Remarks***

This recommendation takes account of:

- Low or high risk of transmission and higher risk of poor outcomes of infection.

**Recommendation 15**: If the likelihood of complications of infection is low, antiviral chemoprophylaxis need not be offered to individuals in 'at risk' groups or health care workers. This recommendation applies independent of risk of human-to-human transmission. **(Weak recommendation, low quality evidence)**

***Remarks***

This recommendation takes account of:

- Low risk of transmission and low risk of poor outcomes of infection.

**Table. Use of Antivirals – Chemoprophylaxis**

| Risk | | Recommendation | Population | Strength of Recommendation |
|---|---|---|---|---|
| **Transmission** | **Complications** | | | |
| High | High | If drug available and virus susceptible, use either neuraminidase inhibitor or M2 inhibitor | Defined target population | Weak |
| | | | Individual patients | Weak |
| | | | Healthcare worker | Weak |
| High | Low | Chemoprophylaxis not recommended | Individual patients | Weak |
| | | | Healthcare worker | Weak |
| Low | High | If drug available and virus susceptible, use either neuraminidase inhibitor or M2 inhibitor | Individual patients | Weak |
| | | | Healthcare worker | Weak |
| Low | Low | Chemoprophylaxis not recommended | Individual patients | Weak |
| | | | Healthcare worker | Weak |

**Other Interventions for Management of Patients with Influenza**

**Recommendation 16**: In patients with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as monotherapy. If ribavirin is to be used in combination with other therapies, this should be done only in the context of prospective clinical and virological data collection.

**Recommendation 17**: In pregnant women with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as treatment or chemoprophylaxis.

**Recommendation 18**: In patients with confirmed or strongly suspected influenza virus infection, immunoglobulins or interferons or other unapproved therapies should not be administered unless in the context of prospective clinical and virological data collection.

**Definitions**:

**GRADE Quality Assessment Criteria**

- **High**: Further research is very unlikely to change the confidence in the estimate of effect.
- **Moderate**: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
- **Low**: Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
- **Very low**: Any estimate of effect is very uncertain.

**Strength of the Recommendations**

**Strong** recommendations can be interpreted as:

- Most individuals should receive the intervention.
- Most well-informed individuals would want the recommended course of action and only a small proportion would not.
- Could unequivocally be used for policy making.

**Weak** recommendations can be interpreted as:

- The majority of well-informed individuals would want the suggested course of action, but an appreciable proportion would not.
- Widely varying values and preferences.
- Policy making will require extensive debates and involvement of many stakeholders.

## CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based primarily on systemic reviews of randomized trials of oseltamivir, zanamivir, amantadine, and rimantadine in the treatment and prophylaxis of influenza. These were supplemented by individual reports of randomized controlled trials not included in the systematic reviews and also by observational studies.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate chemoprophylaxis and treatment ofÂ pandemic (H1N1) 2009 influenza and other influenza viruses

### POTENTIAL HARMS

Systematic reviews indicate that the occurrence of adverse events is generally similar between antivirals and placebo; however, some reviews have shown a significantly greater occurrence of adverse effects with amantadine and rimantadine compared with placebo.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

- Pregnant women and children aged less than 1 year with uncomplicated illness due to influenza virus infection should not be treated with *amantadine* or *rimantadine*.
- In pregnant women with confirmed or strongly suspected influenza virus infection, *ribavirin* should not be administered as treatment or chemoprophylaxis.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- The randomized, controlled trials of antivirals are generally of a high quality in terms of study design, interventions, comparators, outcomes and consistency of results. However, there are currently no clinical trials of available antivirals used in a pandemic situation. Consequently, there is some uncertainty about the applicability of the available evidence to a pandemic situation. While a group of trials can be 'high quality' evidence for one question, because of uncertainty about their applicability or directness, the same trials can be 'very low' quality evidence for a different question.
- There are few head-to-head randomized controlled trials directly comparing antivirals. There are very limited clinical data comparing rimantadine and zanamivir and no published trials comparing oseltamivir and zanamivir directly for chemoprophylaxis. As such, no firm conclusions can be drawn regarding comparative efficacy for the neuraminidase inhibitors. All chemoprophylaxis recommendations are principally based on trials that compare active treatment to placebo and therefore comparisons between treatments are indirect.
- All the recommendations are strongly influenced by patterns of antiviral resistance. Resistance prevalence in circulating influenza strains is collated and reported by World Health Organization (WHO). Recommendations herein, therefore, may need to be modified in the light of current or local knowledge of the antiviral susceptibility of circulating viruses.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Staying Healthy

### IOM DOMAIN

Effectiveness
Timeliness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

World Health Organization (WHO). WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva: World Health Organization (WHO); 2009 Aug 20. 83 p. [23 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2009 Aug 20

### GUIDELINE DEVELOPER(S)

World Health Organization - International Agency

### SOURCE(S) OF FUNDING

World Health Organization

### GUIDELINE COMMITTEE

Not stated

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The following participants declared financial interests related to commercial organizations as listed below:

Del Mar: Technical adviser to GSK <$1000, institutional.

Hay: Technical adviser to GSK <$3000, personal.

Kawaoka: Consulting and research support from Cricell Holland BV, Theraclone Sciences, Chagai Pharmaceuticals, Daiichi Sankyo Pharmaceuticals, Toyama chemical, personal, >$10000; speakers honoraria from Chugai Pharmaceuticals, Novartis, Sankyo, Toyama chemical, Wyeth, GSK, personal.

Monto: Consultant for GSK and Roche, (<$10000), personal.

Tam: Holds shares in Wyeth (>$10000), personal.

Suagya: Technical adviser to Daiicji-Sankyo (>$10000), travel support from Denka Seiken, personal.

Van der Werf: Consultancy and research support from Danone, GSK, Roche to research unit, not personal.

The following participants declared non-financial academic interests related to commercial organizations:

Hayden: Unpaid advisor (with access to confidential information) for Nexbio, Biocryst, GSK, Roche, Toyama, Respirvert, 3V biosciences, Inhibikase, as well as advisor to US government authorities on antivirals.

The following participants declared no interests:

Bautista, Codeco, Chotpitayasunondh, Mardel, Schünemann, Uyeki.

Participants noted that, given their roles as advisers to a number of professional and government bodies in the current pandemic situation, many had made public

statements regarding use of antivirals. These were not considered to be conflicts for the purposes of the meeting.

### GUIDELINE STATUS

This is the current release of the guideline.

### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the World Health Organization Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

### AVAILABILITY OF COMPANION DOCUMENTS

None available

### PATIENT RESOURCES

None available

### NGC STATUS

This NGC summary was completed by ECRI Institute on December 10, 2009.

### COPYRIGHT STATEMENT



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